COMMENTARY

Cancer Survivorship—Genetic Susceptibility and Second Primary Cancers: Research Strategies and Recommendations

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Cancer survivors constitute 3.5% of the United States population, but second primary malignancies among this high-risk group now account for 16% of all cancer incidence. Although few data currently exist regarding the molecular mechanisms for second primary cancers and other late outcomes after cancer treatment, the careful measurement and documentation of potentially carcinogenic treatments (chemotherapy and radiotherapy) provide a unique platform for in vivo research on gene–environment interactions in human carcinogenesis. We review research priorities identified during a National Cancer Institute (NCI)–sponsored workshop entitled "Cancer Survivorship—Genetic Susceptibility and Second Primary Cancers." These priorities include 1) development of a national research infrastructure for studies of cancer survivorship; 2) creation of a coordinated system for biospecimen collection; 3) development of new technology, bioinformatics, and biomarkers; 4) design of new epidemiologic methods; and 5) development of evidence-based clinical practice guidelines. Many of the infrastructure resources and design strategies that would facilitate research in this area also provide a foundation for the study of other important nonneoplastic late effects of treatment and psychosocial concerns among cancer survivors. These research areas warrant high priority to promote NCI's goal of eliminating pain and suffering related to cancer. [J Natl Cancer Inst 2006;98:15–25]

The 5-year relative survival rate after a diagnosis of cancer has increased steadily over the last few decades to reach almost 64% in the mid-1990s *(1)*. As of 2001, there were almost 10 million cancer survivors in the United States, representing 3.5% of the population. Because of advances in early detection, supportive care, and treatment, the number of cancer survivors has tripled since 1971 and is growing by 2% each year *(2)*. This growing and heterogeneous population provides important opportunities for clinical and epidemiologic research into cancer biology, long-term treatment effects, and prevention. One of the most serious events experienced by cancer survivors is the diagnosis of a new cancer. The number of second- or higher-order cancers is burgeoning and accounted for about 16% of incident cancers in 2003 *(1)*. Also, second cancers have become a leading cause of death among long-term survivors of Hodgkin lymphoma *(3–5)*. Second cancers can reflect the late sequelae of treatment; the influence of lifestyle factors, environmental exposures, and host factors; and combinations of influences, including gene–environment and gene–gene interactions (Fig. 1).

The research community has made great strides in elucidating treatment-associated risks for second cancer and documenting dose–response relations between specific chemotherapeutic agents and/or therapeutic radiation and site-specific risk; however, the identification of patient subgroups that might be at heightened susceptibility of developing cancer or other adverse sequelae has not been systematically addressed. Although there are few data on the molecular underpinnings of genetic susceptibility to the development of late effects in the growing population of cancer survivors, the careful measurement and documentation of potentially carcinogenic treatments (chemotherapy and radiotherapy) serve as a strong research platform into the study of gene–environment and gene–gene interactions. To date, however, there has been no concerted effort to provide future research direction in the complex area of molecular mechanisms of second cancer development. Thus, there is a

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See "Notes" following "References."

DOI: 10.1093/jnci/djj001

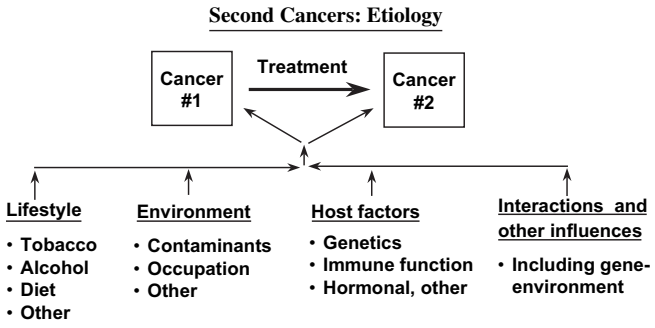

Fig. 1. Risk factors for second primary cancers (refer to text). Many influences, some of which are diagrammed here, may contribute to the development of multiple primary cancers, including interactions between exposures. From Travis LB. Acta Oncologica 2002;41:323–333. Reproduced with permission from Taylor and Francis, Stockholm, Sweden.

lack of relevant clinical research to provide evidence-based patient management guidelines and little consensus on either the infrastructure or study designs needed to comprehensively investigate late effects. Because molecular markers to gauge patient prognosis and predict tumor response to treatment are under investigation *(6–8)*, it seems timely that attempts to customize therapy could also incorporate factors that might predict the susceptibility of patients to both acute and chronic toxicity, including second primary cancers. Prospective identification of patients genetically susceptible to the late complications of cancer treatment *(9)* could result in opportunities to individualize therapy to maximize therapeutic benefit and to minimize serious late toxicity *(10)*. The goal of this commentary is to provide perspective on the research agenda, design considerations, and infrastructure that are needed to understand the underlying genetic mechanisms of late neoplastic effects in cancer survivors and thus to facilitate the development of evidence-based long-term management and intervention strategies. Although the focus of this commentary is largely on second primary cancers, because of their lethality *(3,5,11)*, most of the infrastructural and design approaches that support research in this area also provide a sound basis for the study of other important physiologic late effects and psychosocial concerns in cancer survivors *(12)*.

The current perspective emerged from a workshop entitled "Cancer Survivorship: Genetic Susceptibility and Second Primary Cancers," held November 8–9, 2004, in Rockville, Maryland. The goals of the workshop were to identify research issues, priorities, resources, and infrastructure requirements needed to advance the field of second primary cancers and genetic susceptibility and to make specific recommendations for implementation of new research strategies. The workshop focused mainly on survivors of adult cancers, given the lack of a comprehensive, organized approach in this research area to date. Workshop participants considered inherent genetic susceptibility factors to second primary cancers within the context of familial syndromes, genetic modifiers of specific radiation- and chemotherapy-related cancers, and available populations of cancer survivors to study late effects. The participants represented a transdisciplinary group of experts in epidemiology, statistics, molecular genetics, clinical genetics, pharmacogenomics, informatics, radiation biology, medical oncology, pediatric oncology, and radiation oncology, as well as the advocacy community.

Review of Research Progress

Second primary cancers were categorized according to major identified etiologic influences: syndromic, cancer treatment, and shared etiologic exposures. The categories were recognized as not mutually exclusive, because multiple factors influence the risk of second cancers (Fig. 1), including interactions between treatment and other exposures, such as tobacco use *(13–15)*.

Cancer Syndromes

Some syndromic cancers are associated with nonmalignant phenotypes that identify individuals at increased risk, such as Fanconi anemia or Cowden disease, whereas others exhibit only malignant phenotypes, such as BRCA1- and/or BRCA2-related breast and/or ovarian cancer or Li Fraumeni syndrome *(16,17)*. Some syndromes are autosomal dominant (e.g., Li Fraumeni syndrome and Cowden disease); others are autosomal recessive (e.g., Fanconi anemia, Bloom syndrome, and xeroderma pigmentosum). These syndromes are most recognizable in the familial setting, and the major susceptibility genes for many of these syndromes have been identified. Factors that affect gene penetrance are complex and include the nature and location of the specific mutation and presumed gene–environment and gene–gene interactions. Although hereditary susceptibility explains only a small proportion of all second cancers, an increased risk of primary tumors arising in multiple sites is a distinguishing feature of kindreds carrying germline genetic predispositions *(16)* and can provide unique insights into underlying mechanisms. Selected syndromes reviewed at the workshop are summarized below and include Li Fraumeni syndrome *(18)*, BRCA-related hereditary breast and/or ovarian cancer *(19)*, and Fanconi anemia *(20)*.

In Li Fraumeni syndrome, gene mutation carriers are predisposed to a wide spectrum of tumors, including breast cancer, osteosarcoma, soft-tissue sarcoma, brain tumors, adrenocortical carcinoma, and leukemia *(18)*. Syndrome-associated cancers usually develop at younger-than-usual ages, and affected family members continue to develop metachronous tumors at high frequencies throughout life *(21)*. Germline mutations in the p53 tumor suppressor gene account for this striking phenotype in 70%–75% of Li Fraumeni syndrome families *(22–24)*, although additional predisposition loci have been recently mapped *(25)*. In the last several years, new directions for Li Fraumeni syndrome research have evolved. First, epidemiologic analyses have permitted refinements in the clinical definition of Li Fraumeni syndrome, resulting in more effective identification of potential Li Fraumeni syndrome families *(26)*. Second, several novel effectors and targets of p53 that regulate cellular response to DNA damage have emerged as candidates to explain the multicancer "Li Fraumeni syndrome–like" phenotype in families without germline p53 mutations. Improvements in mutation and functional analysis techniques and the use of oligonucleotide microarray and tissue expression array technologies have begun to shed light on the relevance of low-penetrance p53 mutants in certain Li Fraumeni syndrome phenotypes, as well as the potential for epigenetic phenotype modification *(27)*. Recent evidence suggests that infection with DNA polyomaviruses (e.g., simian virus 40), novel pH-dependent p53 mutants *(28)*, status of the p53 codon 72 polymorphism *(29)*, and DNA repair genes *(30)* may influence the cancer phenotype *(27)*.

The overall burden of the risk of multiple primary cancers associated with the common hereditary breast and colon cancer syndromes is noteworthy. If we assume that there are more than 5 million survivors of breast or colon cancer in the U.S. *(31)*, of which 5%–10 % may be caused by genetic factors *(32)*, up to half a million of these patients may be at risk of secondary hereditary neoplasms. The historic observation of twofold to fivefold increased risks of cancers of the ovary, thyroid, and connective tissue after breast cancer *(33)* presaged the later syndromic association of these tumors with inherited mutations of BRCA1, BRCA2, PTEN, and p53 *(16)*. By far the largest cumulative risk of a secondary cancer in BRCA mutation carriers is associated with cancer in the contralateral breast, which may reach a risk of 29.5% at 10 years *(34)*. The Breast Cancer Linkage Consortium *(35,36)* also documented threefold to fivefold increased risks of subsequent cancers of prostate, pancreas, gallbladder, stomach, skin (melanoma), and uterus in BRCA2 mutation carriers and twofold increased risks of prostate and pancreas cancer in BRCA1 mutation carriers; these results are based largely on self-reported family history information. By use of the technique of direct mutation detection in the Ashkenazim, in whom genotyping is facilitated by the predominance of three founder mutations, the excess risk of prostate and pancreatic cancer was observed only in BRCA2 mutation carriers *(37,38)*, and no increased risk of colon cancer or lymphoma was observed in BRCA1 or BRCA2 mutation carriers *(39,40)*. The markedly elevated rates of secondary breast cancers led to the recommendation of risk-reducing oophorectomy, resulting in a 75% decrease in breast and ovarian cancers and a 3% detection of occult (stage I) ovarian cancers in a prospective cohort study of BRCA mutation carriers *(41)*. Recently, no increased risk of ovarian cancer or other secondary cancer types was observed in a large prospective cohort investigation of hereditary breast cancer kindreds without BRCA mutations, establishing the foundation for evidence-based screening for secondary cancers in this setting *(42)*.

Hereditary nonpolyposis colorectal cancer, which is associated with excess cancers of colon, endometrium, stomach, small intestine, hepatobiliary system, kidney, ureter, and ovary, was linked to germline mutations in a family of DNA mismatch repair genes (e.g., MLH1, MSH2, MSH6) *(43)*. Relationships between cancers of breast, colon, and possibly other sites may also exist through inherited mutations of CHEK2 *(44)*. A recent large study of familial colorectal cancer kindreds without the molecular hallmarks of hereditary nonpolyposis colorectal cancer documented no increased incidence of secondary cancers of the endometrium, stomach, small intestine, hepatobiliary system, kidney, ureter, or ovary *(45)*.

Fanconi anemia is a rare, autosomal recessive syndrome characterized by chromosomal instability, cancer susceptibility, and hypersensitivity to the toxic effects of DNA cross-linking agents, such as mitomycin C. Cancers occurring excessively in patients with Fanconi anemia include leukemia and cancers of the head and neck, vulva, cervix, esophagus, liver, and brain *(17,46)*. The study of Fanconi anemia has recently provided remarkable insights into mechanisms of DNA repair and signaling pathways. Nine of the 11 known Fanconi anemia genes have been cloned (FANCA, B, C, D1 [BRCA2], D2, E, F, G, and L) *(47)*. All known Fanconi anemia proteins cooperate with breast and/or ovarian cancer susceptibility gene products (BRCA1 and BRCA2) in a pathway required for cellular resistance to DNA cross-linking agents. This "Fanconi anemia–BRCA pathway" is a DNA damage–activated signaling pathway that controls DNA repair. Importantly, this pathway is inactivated in a proportion of several types of human cancers, including breast and ovarian cancer, by methylation of one of the Fanconi anemia genes, FANCF *(48)*. These observations suggest a broad and important role of the Fanconi anemia–BRCA pathway in human carcinogenesis.

Treatment-related cancers and genetic susceptibility. A large body of research supports the role of chemotherapy or radiotherapy in the development of second cancers after adult or pediatric cancer *(49)*. Second malignant neoplasms are one of the most serious sequelae of successful cancer treatment and are the leading cause of death in long-term survivors of Hodgkin lymphoma *(3,5,11)*. Analytic studies have documented dose–response relations between radiotherapy for Hodgkin lymphoma and subsequent breast *(50,51)* and lung cancer *(14,15,52)* and between radiation and chemotherapy for breast cancer and lung cancer *(53)* and leukemia *(54)*.

Late effects of treatment may be modified by moderate- or low-penetrance genetic traits or by other gene–environment and gene–gene interactions. The importance of pharmacogenomics has been increasingly recognized, with estimates that genetics contributes 20%–95% of the variability in cytotoxic drug disposition and effects *(55–57)*. Genetic polymorphisms in proteins involved in drug metabolism and transport are clinically relevant, as are variations in genes that encode receptors for target proteins of drugs *(58)* and epidermal growth factor receptor tyrosine kinase inhibitors *(59,60)*. Advances in molecular genetics and pharmacogenomics have linked polymorphisms in genes encoding selected drug-metabolizing enzymes, such as glutathione *S*-transferase, cytochrome P450s, and thiopurine methyltransferases *(61–63)*, with the development of therapy-related cancer. For example, patients who have deficient activity of thiopurine methyltransferase are at increased risk of epipodophyllotoxin-related acute myeloid leukemia *(64)* or irradiation-induced brain tumor *(65)*. In fact, acute myeloid leukemia has been reported in these patients even when treatment consisted primarily of antimetabolites *(66)*. However, none of these factors has absolute sensitivity or specificity as a predictor of later cancer risk, emphasizing that multiple host factors likely predispose individuals to the development of this complication. A recent promising approach is the use of gene expression microarray analysis to perform genomewide searches for possible host genetic risk factors to identify targets involved in therapy-related malignancies in unrelated tissues *(67,68)*.

Sources of pharmacokinetic and pharmacodynamic variability that may influence drug efficacy and toxicity include differences in patient body size and composition, age, race/ethnicity, and sex, as well as physiologic considerations, such as concomitant diseases, the cancer process itself, and hepatic and renal function *(69,70)*. Drug–drug interactions *(71)*, drug formulation interactions, and drug–food constituent interactions must also be considered *(72)*. The importance of pharmacogenomics in drug dosing was recently summarized *(58)*, with attention given to the individualization of chemotherapy for gastrointestinal cancers by McLeod et al. *(73)*.

Because variations in DNA repair appear to play a role in the susceptibility to de novo cancer *(74,75)*, it is likely that they modify cancer risk after exposure to DNA-damaging agents, such as radiotherapy and chemotherapy. There are few data, however, on the role of polymorphisms in DNA repair

genes in modulating susceptibility to therapy-related cancer *(76–78)*. Any specific DNA repair activity must also be considered in the context of the global pathway in which it operates, along with redundancy between various pathways. Further, because DNA repair can have a differential impact on mutation and toxicity at the molecular and cellular level, the ability to independently assess these two endpoints and to determine how they are affected as a function of therapy dose may be essential to understanding DNA repair as a treatment-related modifier of cancer risk.

The possible role of nutritional factors as modifiers of second-cancer risk also merits consideration *(79)*. Several investigations have examined limited aspects of diet's effect on either cancer recurrence, such as the Women's Healthy Eating and Living randomized controlled trial of a high-vegetable, low-fat diet for women with early-stage breast cancer *(80)*, or on second tumor risk after oral and/or pharyngeal cancer *(81)*. However, there have been no comprehensive evaluations of the potentially variable effects of diet before, during, and after cancer therapy or evaluations of their possible interaction with genetic susceptibility to modify second-cancer risk. Candidate dietary components worthy of further evaluation have been comprehensively reviewed in the context of de novo cancer and include essential nutrients (e.g., vitamins and specific fatty acids), major energy sources (e.g., proteins, carbohydrates, and fats), specific food groups (e.g., meats, fruits, and vegetables), food supplements, and others *(82)*.

Retinoblastoma (RB) serves as a prominent example of how genetic mutations can influence the risk of radiotherapy-related cancers. Patients with hereditary RB have germline mutations in the RB-1 gene that predispose them to a high risk of osteosarcomas, soft-tissue sarcomas, melanoma, as well as cancers of the brain, nasal cavities, eye, and orbit; and radiation therapy further enhances the risk of tumors arising in the radiation field *(83)*. The RB gene and others that when mutated increase the susceptibility to radiation damage [e.g., TP53 *(84)* and ATM *(85)*] are important in the cellular response to DNA damage *(86)*. For patients with germline mutations in TP53 (Li Fraumeni syndrome), this sensitivity also confers an increased risk of radiation-associated cancer *(18)*.

Compared with the general population, blood relatives of patients with ataxia-telangiectasia have a statistically significantly twofold elevated risk of breast cancer, with even higher (threefold to fivefold) risks among those younger than 50–55 years *(87,88)*. In general, however, ATM appears to be a weak genetic risk factor for sporadic breast cancer *(88)*, and ATM mutation carriers do not constitute a meaningful proportion of patients with radiation-induced second cancers *(89–91)*.

Other factors that may influence response to radiation exposure include radiation-related genomic instability *(92,93)*, epigenetic phenomena, and bystander effects *(94,95)*. These mechanisms, however, do not necessarily translate into an increased risk of radiotherapy-related second cancers *(96)*. Increasing knowledge of the human genome *(97,98)*, the development of new molecular methodologies *(99,100)*, and the application of proteomics *(101–103)* and related approaches may eventually enable a more comprehensive understanding of radiation-related human cancer, although to date these new technologies have had limited success. An alternative, interim approach is to identify genes involved in DNA repair and/or checkpoint control that are known to be mutated in a small, but notable, proportion of the human population and to study these genes in laboratory animals. For example, mouse embryo fibroblasts from ataxia-telangiectasia heterozygote mice have been shown to be more sensitive to the induction of oncogenic transformation by γ-rays than wild-type cells *(104)*; ataxia-telangiectasia heterozygotes are also more susceptible to the induction of ocular cataracts by γ-rays than wild-type animals *(105)*. These experiments demonstrate that ataxia-telangiectasia heterozygotes are radiosensitive for both a stochastic and a deterministic effect. Another gene of interest is the Rad9 gene, originally identified as an important determinant of radiosensitivity in the yeast *Schizosaccharomyces pombe (106)*. Human and mouse analogues have been identified, and a Rad9-knockout mouse has been developed *(107–109)*; animals heterozygous for pairs of genes, such as Rad9 and ataxia-telangiectasia, that function in the same signal transduction pathway are even more radiosensitive *(110)*.

Nonclonal chromosomal aberrations measured in cultured peripheral lymphocytes *(111)* have been shown to predict de novo cancer risk independently from carcinogenic exposures in several small cohort studies. Chromosomal aberrations likely represent a composite surrogate measure of the effect of many of the influences outlined above—e.g., carcinogen dose; polymorphisms in genes involved in carcinogen metabolism, DNA repair, and genomic stability; and nutritional status. Several studies have shown that various cancer risk factors, such as differences in DNA repair capacity or metabolizing enzymes, have an effect on the frequency of chromosomal aberrations *(111)*. Thus, cytogenetic biomarkers, including classic approaches and newer methods *(112)*, plus assays that measure nonclonal somatic mutations, may have applications in prospective cohort studies of cancer patients, because they likely integrate multiple factors related to risk of secondary malignancies.

Second cancers caused by shared etiologic factors. Tobacco use is one of the major causes of multiple primary cancers, with strong well-established associations with tumors of lung and upper aerodigestive tract (oral cavity, pharynx, larynx, and esophagus) *(113)*. Patients with lung cancer also demonstrate increased risks of cancers of lip, bladder, and second primary lung cancers *(114),* indicating the shared etiologic role of tobacco use. Often, increased reciprocal risks of lung cancer follow first primary cancers at these other sites *(113)*. Risk is also influenced by whether patients continue to smoke after development of a first smoking-related primary cancer *(115)*. Other tobacco-related cancers include those of pancreas, bladder, kidney, and leukemia *(116)*. Alcohol intake is causally related to upper aerodigestive tract cancers, as well as tumors of liver, breast, and colorectum *(117,118)*. Synergistic effects for tobacco and alcohol exist for upper aerodigestive tract cancers *(119)*.

Endocrine and dietary factors influence the aggregation of cancers of breast, uterine corpus, ovary, and colon, although for some of these cancers genetic factors are also operative *(120)*. In general, for cancers that share etiologic factors, pertinent genetic traits will likely have low to moderate penetrance and be driven by multiple gene–environment and gene–gene interactions.

Discussion and Recommendations: Future Research Directions

The research issues, priorities, resources, and infrastructure requirements needed to advance the field of genetic susceptibility

and second primary cancers, and specific recommendations for implementation of new research strategies, are summarized below.

Infrastructure

Various types of cohorts are needed to study each category of second cancers summarized above. Each cohort requires rigorous definition, acquisition of specimens for high-quality genotyping and for tumor phenotyping, and high-quality exposure data. Data on diet and supplement use—before cancer diagnosis, during therapy, and after completion of therapy—should also be collected to examine any role of dietary factors in modification of second cancer risk. Existing resources that might provide the necessary infrastructural requirements as reviewed above include major cancer centers, National Cancer Institute (NCI)–sponsored clinical trial cooperative groups, and population-based cancer registries.

Multicenter adult cancer survivor cohort. There was a high level of enthusiasm at this workshop for the development of a multicenter cancer survivor cohort derived from large cancer institutions. Several major centers have independently begun their own cancer survivorship programs. The Harvard Affiliates (Brigham and Women's Hospital, Dana-Farber Cancer Institute, Beth Israel Deaconess Medical Center, and The Children's Hospital) have a Hodgkin lymphoma database that dates back to 1969 *(121–123)*. The Living Well After Cancer Program at the University of Pennsylvania and Children's Hospital of Philadelphia focuses on the needs of patients surviving cancers of breast or testis or childhood cancer (http://www.pennhealth.com). Programs at Memorial Sloan-Kettering Cancer Center include services directed toward counseling and support, screening and wellness, and genetic testing *(124)*. Comprehensive programs for cancer survivors at the University of Texas M. D. Anderson Cancer Center include annual conferences and quarterly newsletters (http://www.mdanderson.org/departments/lacc).

In most institutions, the status of adult cancer patients is routinely updated through hospital-based tumor registries. Detailed information with regard to cancer diagnosis and exposure data (radiation therapy and chemotherapy) is available and of high quality. Opportunities exist to prospectively collect biologic specimens (peripheral blood and tumor and normal tissue from target organ) from subjects at high risk of second cancers or from patients with multiple primary cancers at presentation. The limitation of each program is the relatively small sample size; only a multicenter effort would have sufficient statistical power to address the role of gene–environment interactions in the late effects of treatment and provide definitive guidance for evidence-based patient management strategies. The goal is the establishment of programs at multiple centers using common infrastructure, common data collection instruments (including self-administered food-frequency questionnaires), and common state-of-the-art biospecimen collection, processing, storage, and distribution systems, in support of hypothesis-generating and hypothesis-testing research. Optimally, this system would also support intervention trials aimed at reducing risks of late effects and identify cost-effective strategies for patient follow-up. One model for the development of such a consortium is the Childhood Cancer Survivors Study *(125)* (http://www.cancer.umn/ccss).

The establishment of effective transdisciplinary cancer survivorship programs requires dedicated clinical and research teams. In the Living Well After Cancer Program (www.pennhealth.com), a multidisciplinary team of clinicians (including medical oncologists, radiation oncologists, clinical oncology nurse practitioners, nutritionists, cardiologists, cancer rehabilitation specialists, psychiatrists, and psychologists) and researchers (including those focused on genomics, cancer biology, epidemiology, biostatistics, and behavioral science) integrate the clinical and research arms of the program. An institutional review board–approved clinical research protocol monitors data on symptoms, follow-up, and quality of life; provides feedback to care providers regarding these issues on individual patients; and coordinates the recruitment of patients into studies. Workshop participants emphasized the importance of dedicated staff and the need to budget for the costs of screening, etc. in developing these resources.

Clinical trial cooperative groups. These NCI-sponsored groups represent an important alternative source of data to elucidate the etiology of second cancers. Advantages include the existence of large cohorts of cancer patients, treated (at least initially) in a relatively uniform manner, monitored aggressively for the outcomes of interest, and positioned to obtain either germline or somatic DNA for genotyping. However, the study of late complications of cancer therapy has not, in general, been a high-priority focus for cooperative groups, except in the pediatric setting. Further, these cohorts do not routinely collect detailed information on treatment after first relapse, and follow-up is often not funded beyond the 5 years needed to address the primary treatment question. Finally, patients with multiple primary cancers are routinely excluded from most clinical treatment trials. Despite these obstacles, workshop participants felt that cooperative group resources could be mobilized to support second-cancer studies and to yield important information for a wide spectrum of clinical and scientific endpoints, including long-term treatment outcome, survival, and complication rates for neoplastic and nonneoplastic sequelae.

Workshop participants recommended that an inventory of NCI-sponsored phase III clinical trials be prepared to facilitate identifying populations suitable for testing specific hypotheses. This inventory would include name of the sponsoring cooperative group, protocol number, cancer site treated, specific treatments evaluated, number of subjects enrolled in each arm, and whether germline DNA (or tumor blocks) were collected and stored. Workshop participants also recommended that the capacity of NCI cooperative groups be enhanced to collect data on nutritional, lifestyle, occupational and medical exposures, family history, long-term (>5 years) follow-up information, and biospecimens.

Population-based cancer registries. Well-defined cohorts derived from population-based cancer registries have been used successfully to evaluate which second cancers occur in excess after specified first primary malignancies and to provide a valuable starting point for nested case–control studies that evaluate treatment effects in detail *(49,126,127)*. Strengths of registry-based strategies include large sample sizes, which allow the detection of even small increases in the risk of second cancers, and the evaluation of long-term trends according to site, sex, age at exposure, and attained age. Further, the observed and expected numbers of cancers are derived from the same population. Weaknesses of registry-based cohort studies include the limited availability of treatment data and underreporting of second cancers if patients leave registry catchment areas.

Other populations. New cohorts could be developed based on eligibility criteria that enrich study populations for those at

high risk of second cancers. Such criteria include specific cancer treatments previously demonstrated to carry a high risk of second cancers [e.g., high-dose, extended-field radiation therapy for Hodgkin lymphoma *(121)*]; long-term, high cumulative doses of alkylating agents *(128–129)*; a specific clinical phenotype at the time of the first cancer diagnosis that might increase the risk of treatment-related cancer (e.g., nevoid basal cell carcinoma syndrome); the presence of field effects in normal tissues that represent an increased risk; or specific genetic traits. Workshop participants expressed concern regarding the potential risk of second cancers and other late effects associated with new treatment modalities such as intensity-modulated radiotherapy that exposes a larger volume of normal tissue to low doses of radiation *(130)* and encouraged the prospective formation of patient cohorts for follow-up. Other recommendations for future research regarding the long-term effects of cancer and its treatment, including follow-up of patients treated with radioimmunoconjugates *(131)*, have been comprehensively reviewed previously *(13)*.

Other Considerations

Recommendations for evidence-based follow-up care. The implications for research opportunities in large cohorts of cancer survivors include, importantly, the provision of definitive recommendations for evidence-based care. Pilot studies of interventions to prevent second cancers within genetically defined high-risk groups should be undertaken. Moreover, smoking cessation programs in all cancer survivors should be emphasized. This specific intervention is likely to be cost effective in both the prevention of second primary smoking-related cancers *(115)* and with regard to the improvement in general well being.

Involvement of cancer survivors. Workshop participants encouraged continued patient involvement in decisions regarding initial cancer treatment and long-term follow-up care *(132)* and the development of strong relationships between hospitals and advocacy groups, such as the National Coalition for Cancer Survivorship (http://www.canceradvocacy.org). Patients are also receptive to the use of information from electronic medical records for research purposes provided consent is first obtained *(133)*. Many survivorship programs offer Web-based education informatics for patients; and the further development of these resources *(134)* to collect long-term follow-up data on large numbers of patients was enthusiastically supported by workshop participants.

Study Design

The application of traditional cohort and nested case–control designs to studies of treatment-related second primary cancers was recently reviewed *(127)*, with special attention given to smoking-related cancers in a separate report *(113)*. Whereas standard methods have proven highly effective in defining dose–response relations between treatment and second cancer risk, new analytic paradigms are needed to explore gene–environment and gene–gene interactions *(135)*. For case–control studies, these include countermatching on therapy in studies where both treatment and genetic susceptibility may play important roles *(135)*. In general, new hypothesis paradigms and customized research methods are needed to more efficiently study the various determinants of both second cancers and other late effects. A summary of design issues related to future studies follows.

Cohort studies. An inherent strength of the cohort design is the ability to efficiently investigate multiple endpoints related to cancer survivorship, including second cancers, in the same population. It is essential for such cohorts to be of sufficient size for adequate statistical power, and procedures must be put into place to ensure complete ascertainment of relevant endpoints. Rigorous follow-up mechanisms should trace patients over long periods, and sufficient biospecimen quantities from appropriate sources should be collected and stored. To further study tissue field effects of carcinogens, such as tobacco and alcohol, specific molecular studies of normal tissue can be conducted when adequate surgical specimens are available. Because tumor tissue is increasingly being collected after neoadjuvant therapy, mechanisms are needed to procure pretreatment tissue for future study.

Case–control studies. Case–control studies are especially advantageous for evaluating factors that are rare but that confer high risk, such as strong genetic variants *(136)*, because they permit population-based epidemiologic evaluation when conventional case–control studies are infeasible. A prototype study of the role of CDKN2A mutations in melanoma was recently completed (Berwick M, Orlow I, Hummer A, Armstrong BK, Kricker A, Marrett LD, et al., unpublished data). Case identification and decisions with regard to study inclusion and exclusion criteria must be carefully considered, as should the various options regarding control selection (noncancer, same type of cancer as the first or second, matched on age at diagnosis or length of follow-up, and so forth). Depending on the research question, population-based, family-based, or large center-based designs may be more appropriate.

Family studies. Cohorts of family members from kindreds at high risk of specific cancers have been essential for the identification of high-risk susceptibility genes. After a specific high-risk gene has been identified, these kindreds can also be a source of gene carriers to 1) estimate penetrance in high-risk families, 2) evaluate the role of environmental factors and variations in modifier genes as determinants of differences in penetrance, 3) estimate risk of multiple cancers in gene carriers, and 4) develop appropriate targeted interventions to decrease cancer risk. Information learned from these kindreds about tumor pathogenesis and progression often translates to sporadic cancers. However, independent estimates of penetrance must also be obtained from groups more representative of the general population, because estimates for specific cancers from high-risk families will, by definition, be inflated. When founder mutations are identified in specific populations, cost-effective screening can identify less biased groups of gene carriers for studies of penetrance, modifiers of penetrance, and intervention studies.

New Technologies, Biospecimen Collection, and Bioinformatics

The emergence of new technologies for the analysis of genetic alterations, both germline and somatic (restricted to available tumor tissue), will be critical to the determination of the genetic contributions to second-cancer risk. Specifically, the assessment of germline variants can be analyzed on new genotype platforms at higher densities and, soon, across the entire genome *(137)*. In parallel, new developments will accelerate the rate of sequencing of both common and rare variants. Assessment of the latter will require corroborative functional or pedigree studies. Sequence analysis of normal and tumor tissue may also identify mutations

that could be signatures of second cancers and that could be used for therapeutic or preventive interventions. Central databases are needed to report frequencies of variants in reference sets of DNA, such as the SNP500cancer (http://snp500cancer.nci.nih.gov) and International HapMap (http://hapmap.org) *(138,139)*.

High-quality biospecimen collection and storage infrastructure is essential to any research enterprise. Strategies that reduce costs and enhance biospecimen quality, collection, processing, storage, and distribution are urgently needed. Efforts aimed at reducing the amount of tissue and DNA needed for various assays should also be undertaken. When the amount of DNA available is limiting, standardization of protocols for whole-genome amplification should be put into place, because of concerns regarding amplification fidelity in specific regions of the genome *(140)*.

As new technologies simplify the generation of large genetic data sets, bioinformatic solutions are required specifically to provide analytic tools for comparing datasets and for determination of genes already evaluated *(141)*. A centralized biospecimen collection or tracking system should be created to permit sample retrieval from multiple repositories (i.e., a virtual centralized repository). Procedures should include access to multiple tissues including blood (or other DNA sources), normal tissue from the target organ, and tumor tissue. Workshop participants recognized that major logistic and cost issues would be involved in such an undertaking, including comparability of documentation, lab procedures, quantification of reagents, types of specimens, as well as the need for scientific review for specimen use and for issues related to control of specimens. The NCI Center for Bioinformatics provides resources that might fulfill the bioinformatics infrastructure needs of a cancer survivorship research network. Procedures already developed by the NCI Center for Bioinformatics for other translational projects allow collaborative scientific interactions between basic science and clinical investigators and facilitate the rapid translation of novel basic and/or preclinical research into clinical settings. This prototype might be adaptable to survivorship network needs with a small incremental investment, thus providing a critical framework for longitudinal studies of the late effects of cancer treatment.

Molecular profiling of tumors will be necessary, as illustrated by seminal studies in breast cancer *(142)* and non-Hodgkin lymphoma *(143)*. The more precise molecular classification of tumors provides an opportunity to analyze etiologic pathways and therapeutic targets. The molecular basis of how carcinogenic field effects translate into increased second cancer risks is also poorly understood. Several available technologies that should be applied to tumor and normal tissue profiling currently include microarray analysis (e.g., detection of mRNA, comparative genomic hybridization, and hypermethylation of promoter regions), high-throughput somatic mutation analysis, and proteomics.

Summary of Consensus Points: Research Priorities

In small-group and full workshop discussions, participants identified research issues, gaps, priorities, and resources needed

Table 1. Workshop recommendations for future research: genetic susceptibility and second primary cancers

1. Develop research infrastructure for studies of cancer survivorship
   - Institute a systematic, national approach to develop research infrastructure for studies of genetic modifiers of late effects of cancer treatment, including second malignancies.
   - Provide for rigorous ascertainment of multiple primary cancers with clinical annotation, detailed treatment data, and biospecimen collection.
   - Establish multicenter cohorts of cancer survivors, with recruitment of transdisciplinary research teams dedicated to research the late effects of therapy.
   - Expand the capacity of National Cancer Institute cooperative groups to ascertain and study long-term outcomes in clinical trial populations, in support of survivorship research.
2. Create a coordinated system for biospecimen collection
   - Standardize biospecimen collection, laboratory procedures, and documentation for blood and other DNA sources, normal tissue from target organs, and tumor tissue.
   - Develop a centralized biospecimen repository or a tracking system ("virtual repository") to permit sample retrieval from multiple storage centers.
   - Institute mechanisms for scientific review of specimen use and administrative procedures for specimen control.
   - Support methodologic research to enhance the quality and lower the cost of biospecimen collection, processing, storage, and distribution.
3. Promote the development of new technology, bioinformatics, and biomarkers
   - Identify new technologies for the analysis of germline and somatic genetic alterations to determine their contributions to second cancer risk.
   - Reduce the amount of tissue and DNA needed for various assays, with standardization of protocols for whole-genome amplification.
   - Develop molecular profiles of tumors that incorporate analyses of etiologic pathways and therapeutic targets related to second cancers and other late outcomes.
4. Support the development of new epidemiologic methods
   - Develop efficient epidemiologic study designs to investigate the role of genetic susceptibility to multiple primary cancers, including genetic modifiers of risk associated with treatment effects or other etiologic factors.
   - Develop optimal approaches for selection of controls for case–control studies in which both treatment and genetic susceptibility play important roles.
   - Include a biospecimen component in all study designs.
5. Develop evidence-based clinical practice guidelines
   - Implement pilot studies of interventions to prevent second cancers within genetically defined, high-risk groups of patients.
   - Integrate smoking cessation programs into research designs.
   - Support research to provide evidence-based follow-up care for cancer survivors.

to advance the area of genetic susceptibility and second primary cancers and made specific recommendations for their implementation. These recommendations spanned five major categories (Table 1). Workshop participants emphasized that second malignancies are part of a broad spectrum of long-term outcomes representing complications of cancer and its treatment and that survivors of adult cancer continue to warrant high research priority to support NCI's goal of eliminating pain and suffering related to cancer *(144)*.

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Notes

Editor's Note: Dr. Pui is a member of the speaker's bureau for Sanofi-Aventis.

We are indebted to the NIH Office of Rare Diseases for providing the funding for this workshop. The workshop and report preparation were also supported by the Intramural Research Program of the NIH, National Cancer Institute, Division of Cancer Epidemiology and Genetics. Dr. Ching-Hon Pui is supported by the American Lebanese Syrian-Associated Charities, the American Cancer Society F.M. Kirby Clinical Research Professorship, and the NCI Cancer Center Core Grant CA-21765.

We thank Ms. Ursula Leitzmann and Mr. Jose Reyes of NCI for providing logistic support, and Ms. Denise Duong of NCI for typing assistance.

Manuscript received June 23, 2005; revised October 17, 2005; accepted October 18, 2005.